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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/284,424	04/09/1999	HANS P. ALBRECHT	5500-01-TMC	2300

7590 10/22/2002

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EXAMINER
MAIER, LEIGH C

ART UNIT	PAPER NUMBER
1623	28

DATE MAILED: 10/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/284,424	Albrecht et al
Examiner	**Art Unit**
Leigh Maier	1623

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *pre-amendment filed July 10, 2002*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-8, 10-30, 34, 38-41, and 44-54* is/are pending in the applica

4a) Of the above, claim(s) _____ is/are withdrawn from considera

5) ☒ Claim(s) *34, 38-41, and 44-51* is/are allowed.

6) ☒ Claim(s) *1, 2, 4-8, 10-12, 16-18, 20-30, and 52-54* is/are rejected.

7) ☒ Claim(s) *3, 13-15, and 19* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 21
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of the Claims

Claims 1, 17, 18, 20, and 34 have been amended. Claims 52-54 have been added. Claims 1-8, 10-30, 34, 38-41, and 44-54 are pending. Any objection or rejection not expressly repeated have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Prosecution Application

The request filed on October 23, 2001 (with missing parts entered April 30, 2002, and pre-amendment filed July 30, 2002) for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/284,424 is acceptable and a CPA has been established. An action on the CPA follows.

Claim Rejections - 35 U.S.C. § 112 - first paragraph

Claims 1-8, 10-30, 52 and 53 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Amended claim 1, and new claims 52 and 53 have introduced a new variable, R^7, with the definition of this variable being

"H, $-S-(C_1-C_6-alkyl)$, or $-SO_2-(C_1-C_6-alkyl)$." The examiner does not find any support for a tri-substituted nitrogen at this position in the specification as originally filed.

Claim Rejections - 35 U.S.C. § 112 - second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8, 10-30, and 54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 includes a proviso excluding several specific compounds. The definition of the variables have been amended to delete heterocyclic moieties as being drawn to non-elected subject matter. However, the list of excluded compounds comprises heterocyclic compounds. Therefore, it is not clear if their inclusion is an oversight or if heterocyclic compounds are indeed meant to be included in formula I of the claim. Furthermore, an adamantyl compound is also included in this proviso. However, the definition of "cycloalkyl" in the specification at page 40, lines 14-15, is limited to monocyclic moieties, and an adamantyl moiety does not appear to be included in this definition. The structural formula of claim 1 does not appear to comprise these heterocyclic/adamantyl compounds, but they are expressly excluded thus rendering the claims vague and indefinite.

Further regarding claim 17, the claim recites R^1 is benzyloxycarbonyl, followed by several choices for R^3. However, in limiting R^1 to benzyloxycarbonyl, R^3 is thereby defined as "benzyl"--or (CH_2)-phenyl -- and cannot also be the other moieties listed in the claim. The claim is thus rendered vague and indefinite.

Regarding claim 54, the third line from the last recites "R^7 is H, $-S-(C_1-C_6-alkyl)$, or $-SO_2-(C_1-C_6-alkyl)$;". However, there does not appear to be a variable R^7 in the forgoing claim. It is not clear if this definition was included by mistake or if the variable was inadverdently omitted. The claim is thus rendered vague and indefinite.

Claim Rejections - 35 USC § 102

. Claims 1, 2, 4, 5, 10, 18, 20, and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by DOLLE et al (EP 623592). DOLLE discloses compounds of fomula I. See examples 2-5, 9-16, 18, 20, 21, 23, 25-27, and 30-32.

Claims 1, 10, 11, and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by MJALLI et al (Biorg. Med. Chem. Lett., 1994). MJALLI discloses a compound of formula I of claim 1. See compound 3c in the reaction scheme at page 1966. The compound is not labeled as such, but is the t-butyl ester of compound 4c. See Table 1.

Claims 1, 10, 11, 30, and 54 are rejected under 35 U.S.C. 102(b) as being anticipated by THORNBERRY et al (Biochem., 1994). THORNBERRY discloses compounds of the structural formulas recited in the claims. See compounds 1, 2, and 4-9.

Claims 1, 10, 11, 30, and 54 are rejected under 35 U.S.C. 102(b) as being anticipated by CHAPMAN et al (US 5,430,128). CHAPMAN discloses compounds consistent with the structural formula recited in the claims. See col 8, lines 23-29 and compounds depicted in col 14-18.

Claims 1, 10, 16, 21, 30, and 54 are rejected under 35 U.S.C. 102(b) as being anticipated by HENG et al (EP 618223). HENG discloses compounds consistent with the structural formulas depicted in the claims. See compounds 31, 43-45, 48-55, 58-63, 79-86, 90, and 91. The reference further teaches the administration of an effective amount of one of the compounds to inhibit ICE. See page 19, lines 41-49.

Claim Rejections - 35 U.S.C. § 103

Claims 1, 2, 4, 5, 8, 10-12, 21, 23-27, 30, 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over CHAPMAN et al (US 5,430,128).

CHAPMAN teaches as set forth above. The reference differs from the instant invention in ways set forth below.

Regarding claims 2, 4, 5, and 8, CHAPMAN exemplifies only an alloc group at this position. See the reaction scheme at col 9-10 and description thereof. However, the R^1s required in claims 2, 4, 5, and 8 are amino acid protection groups known in the art. It would have been obvious to one having ordinary skill in the art to substitute any known amino acid protecting group for the art-disclosed utility in preparing ICE inhibitors. Variation of protecting groups is within the scope of the artisan.

Regarding claim 12, the reference exemplifies a compound wherein R^2 is phenyl. The reference does not specifically exemplify a naphthyl moiety at this postion. However, the reference teaches the substitution of a naphthyl moiety at this position. See definition of R^2 at col 3-4. (This definition teaches substituted naphthyl, but unsubstituted phenyl is exemplified and the artisan would reasonably expect that unsubstituted naphthyl would have similar utility.) It would have been obvious to one having ordinary skill in the art to substitute naphthyl at this position for its art-disclosed utility as an ICE inhibitor.

Regarding claims 21 and 23-27, CHAPMAN teaches that the disclosed compounds have utility as ICE inhibitors and are useful in the treatment of diseases related to this enzyme. See abstract; col 2, lines 35-61; col 8, lines 30-44; paragraph bridging col 10-11; and col 13, lines 21-47. Although the reference does not specifically exemplify treatment, it would have been obvious to one having ordinary skill in the art at the time the invention was mad to use the compounds described for this purpose with reasonable expectation of success.

Regarding claims 52 and 53, all of the compounds exemplified in the reference are ones wherein R^{5a} is propionylphenyl which is specifically excluded by the claim. However, R^{5a} corresponds to R^1 in CHAPMAN when AA_1 is a single bond. (Exemplified compounds are those *not* containing tyrosine as a third amino acid.) It would have been obvious to one having ordinary skill in the art at the time the invention was made to substituted any moiety in the defintion of R^1 for its art-disclosed utility with a reasonable expectation of success.

Regarding independent claims 1 and 52-54 in general, CHAPMAN exemplifies a limited set of compounds in the reference. However, the reference expressly suggests the preparation of many more compounds via a simple change at R^1, AA_1, AA_2, AA_3, or R^2. One of ordinary skill would be motivated to prepare these other compounds for their art-disclosed utility.

Claims 1, 10-12, 16, 21, 24-28, 30, 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over HENG et al (EP 618223).

HENG teaches as set forth above. The reference differs from the instant invention in ways set forth below.

Regarding claims 11 and 12, the compounds exemplified in the reference have substituted phenyl groups at this position. It would have been obvious to one having ordinary skill in the art at the time the invention was made to substitute an unsubstituted pheny or naphthyl at this position, as the reference expressly suggests this substitution. The artisan would be motivated to prepare these compounds for their art-disclosed utiltity with reasonable expectation of success.

Regarding claims 24-26 and 28, the reference does not exemplify the treatment of the specific diseases recited in the claims. However, the reference specifically suggests their utility for these methods. See text starting page 19, line 50, continuing through page 20, line 22. One of ordinary skill would reasonably expect success in using these compound for treating these diseases.

Regarding claims 52 and 53, all of the compounds exemplified in the reference are ones wherein R^{5a} is benzyloxycarbonyl which is specifically excluded by the claim. However, R^{5a} corresponds to R in HENG. It would have been obvious to one having ordinary skill in the art at the time the invention was made to substituted any moiety in the defintion of R for its art-disclosed utility with a reasonable expectation of success. The reference expressly suggests the use of any known amino acid protecting group. See page 4, lines 2-11.

Regarding independent claims 1 and 52-54 in general, HENG exemplifies a limited set of compounds in the reference. However, the reference expressly suggests the preparation of many more compounds via a simple change at R, A_1, A_2, or Y_1. See, particularly, all of page 2; page 6; and page 7, lines 13-20. In addition to having 2 amino acids adjacent to the aspartic acid residue, HENG teaches dipeptide mimics, such as naphthylsulfonyl and cycloalkyl groups at this position. One of ordinary skill would be motivated to prepare these other compounds for their art-disclosed utility.

Claims 1, 2, 4-8, 10-12, 17, 18, 20, 30, 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over DOLLE et al (EP 623592).

DOLLE teaches as set forth above. The reference differs from the instant invention as set forth below.

Regarding claims 6 and 7, the reference does not exemplify compound wherein R^1 is N-acetyl-alanine (valine). Example 18 (23) is a compound wherein R^1 is N-methoxycarbonyl-alanine (valine). However, it would be obvious to substitute any well-known amino acid protecting group, such as acetyl, for its art-disclosed utility. Variation of protecting groups is suggested by the use of different protecting groups in the examples.

Regarding claim 8, the reference does not exemplify compound(s) wherein R^1 is benzoyl. However, it would be obvious to substitute any well-known amino acid protecting group at this position, such as benzoyl, for its art-disclosed utility. Variation of protecting groups is suggested by the use of different protecting groups in the examples.

Regarding claims 11, 12, 17, and 52-54, the compounds exemplified in the reference have substituted phenyl groups at this position. It would have been obvious to one having ordinary skill in the art at the time the invention was made to substitute an unsubstituted phenyl or naphthyl at this position, as the reference expressly suggests this substitution. See definition of R^3 at page 4, lines 12-37. The artisan would be motivated to prepare these compounds for their art-disclosed utiltity with reasonable expectation of success.

Claims 1, 21, 24-28, and 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over DOLLE (EP 623592) as applied to claims 1, 2, 4, 5, 10, 18, 20, and 30 above, and further in view of HENG (EP 618223).

DOLLE teaches as set forth above. The compounds exemplified by DOLLE are esters disclosed to be intermediate precursors to the equivalent carboxylic acid. They are not described as having therapeutic utility.

HENG teaches as set forth above. The reference teaches ICE inhibitors similar in structure to those of DOLLE. HENG further teaches that pro-drugs, such as esters and amides, have utility as ICE inhibitors.

Regarding claims 21 and 24-28, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use these ester pro-drugs for use as ICE inhibitors in the treatment of the diseases recited in the claims with a reasonable expectation of success.

Regarding independent claims 1 and 52-54 in general, DOLLE exemplifies a limited set of compounds (carboxylic acids) in the reference which have been specifically excluded by proviso. However, the reference expressly suggests the preparation of many more compounds via a simple change at R_1, R_2, A, or R_3. See definitions of these variables at pages 4-6. One of ordinary skill would be motivated to prepare these other compounds for their art-disclosed utility.

Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over HENG et al (EP 618223) as applied to claims 1, 10, 16, 21, 30, and 54 above, and further in view of SPRUCE et al (US 6,004,933).

HENG teaches as set forth above. The reference does not teach the compounds as inhibitors of caspase-4.

SPRUCE teaches that ICE is a member of the caspase family and that caspase enzymes are implicated in the same diseases as ICE. See col 1, lines 20-59.

It would have been obvious to one of ordinary skill in the art to use the compounds disclosed by HENG as caspase-4 inhibitors. One of ordinary skill would have a reasonable expectation of success in such a use because of the similarity of the enzymes and the fact that they are implicated in the same family of diseases.

Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over HENG et al (EP 618223) as applied to claims 1, 10, 16, 21, 30, and 54 above, and further in view of BEMIS et al (US 5,843,904).

HENG teaches as set forth above. The reference does not teach the compounds in the treatment of shigellosis.

BEMIS teaches that ICE inhibitors have utility in the treatment of shigellosis. See abstract and col 20, lines 43-67.

It would have been obvious to one having ordinary skill in the art to use the ICE inhibitors taught by HENG to treat shigellosis with a reasonable expectation of success, as BEMIS had taught their utility in this method.

Allowable Subject Matter

Claims 3, 13-15, and 19 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 34, 38-41, and 44-51 are allowed. The references discussed above specifically exemplify and expressly suggest a number of compounds as ICE inhibitors. However, none of the references of record teach or fairly suggest the modification of compounds wherein the compounds comprise at least one unsubstituted methylene group directly adjacent to the carbonyl of the structural formula in claim 50. The specific compounds recited appear to have this structural modification and would also be considered nonobvious.

Examiner's hours, phone & fax numbers

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leigh Maier whose telephone number is (703) 308-4525. The examiner can normally be reached on Tuesday, Wednesday, or Friday 7:00 to 3:30 (ET).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson (703) 308-4624, may be contacted. The fax phone number for Group 1600, Art Unit 1623 is (703) 308-4556 or 305-3592.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-1235.

Visit the U.S. PTO's site on the World Wide Web at http://**www.uspto.gov**. This site contains lots of valuable information including the latest PTO fees, downloadable forms, basic search capabilities and much more.

Leigh C. Maier
Patent Examiner
October 18, 2002